Office Action, p. 3, subpart 8.

Both claims depend from claim 1. Claim 7 specifies that the matrix recited in claim 1 can be, *inter alia*, collagen. Claim 8 specifies that the matrix is collagen. According to the Examiner, claim 1 would exclude collagen as a matrix because the claim states that the matrix cannot be demineralized bone, which, according to the Examiner, consists primarily of collagen.

Applicants respectfully traverse the objection. "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112, 4th ¶. Collagen exists in many forms, one of which being demineralized bone. Claim 1 explicitly states that the recited matrix cannot be demineralized bone. Thus, the collagen matrix recited in claim 7 or 8 should be construed as being in any form but the demineralized bone form. Claims 7 and 8 are properly dependent from claim 1.

Rejection Under 35 U.S.C. § 112, 1st ¶

Claims 1-10, 14-16, 20-23, 32, 33, 35, and 36 are rejected for alleged lack of enablement. Specifically, the Examiner alleges that "the specification discloses at most carboxymethyl cellulose" and fails to teach how to make structurally unrelated compounds having the desired activity or how to identify structural features essential for the desired activity. Office Action, p. 4, lines 4-10. In conclusion, the Examiner states that "[t]he disclosure of a single species of 'binding agent' is clearly insufficient support . . . for claims which encompass any and all 'binding agent'." (Office Action, p. 4, lines 14-15; emphasis added).

Applicants respectfully disagree. First of all, the specification discloses much more than just "a single species" of binding agents. At page 7, lines 11-15, the specification states that "cellulosive derivatives are preferred. . . . Other suitable binding agents include other cellulose gums, sodium alginate, dextrans and gelatin powder." Claim 10 as originally filed also states that binding agents useful in this invention can be "mannitol, dextrans, white petrolatum, mannitol/dextran

combinations, mannitol/white petrolatum combinations, sesame oil, alkyl celluloses, and admixtures thereof."

In addition, the specification identifies the desired characteristics of the binding agents:

> With respect to binding agents, the instant devices preferably comprise agents useful as viscosity-increasing, suspending and/or emsulfying [sic; should read emulsifying] agents. (page 7, lines 10-11)
>
> Among the characteristics of a preferred binding agent is an ability to render the device: pliable, shapeable and/or malleable; injectable; adherent to bone, cartilage, muscle and other tissues; resistant to disintegration upon washing and/or irrigating during surgery; and, resistant to dislodging during surgery, suturing and post-operatively, to name but a few. (page 8, lines 7-11)

See also the specification at page 24, lines 10-17 and at page 25, lines 1-13.

Lastly, the specification teaches how to test the usefulness of a given material as a binding agent. At page 50, line 17, through page 51, line 21, the specification describes methods for testing the integrity, viscosity, appearance, pH, and other characteristics of a binding agent.

Given this ample guidance, a person of ordinary skill in the art can readily identify useful binding agents additional to those exemplified in the specification. The 112, 1st ¶ rejection should be withdrawn.

Rejection Under 35 U.S.C. § 112, 2nd ¶

Claims 2, 3, and 20-23 are rejected as allegedly indefinite. Office Action, p. 5, lines 1-8.

With respect to claims 2 and 3, the Examiner states that the term "conservative amino acid sequence variants" is unclear. Applicants respectfully traverse. It is well known in the art what a conservative amino acid sequence variant is -- it is a sequence with conservative or acceptable amino acid substitutions in reference to the parent sequence. See, e.g., the specification at page 23, lines 8-15:

> Examples of conservative variations include the substitution of one hydrophobic residue, such as isoleucine, valine, leucine or methionine, for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, and the like. The term "conservative variation" also includes the use of a substituted amino acids in place of an unsubstituted parent amino acid, provided that antibodies raised to the substituted polypeptide also immunoreact with the unsubstituted polypeptide.

See also the specification at page 27, lines 12, through page 28, line 3.

With respect to claims 20-23, the Examiner states that it is unclear as to whether the term "w/w" is in reference to the device, the BMP, the carrier, the binding agent, or the matrix. In view of this comment, applicants have amended the claims by deleting "(w/w)" after the one part material; consequently, it is now clear that the reference ingredient for the w/w ratio is the one part material. Thus, in claims 20-22, the w/w ratio is with respect to the binding agent; in claim 23, the w/w ratio is with respect to the matrix.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-5, 7, 15, 20, 22, and 23 stand rejected as allegedly anticipated

by Sato et al. ("Sato"), Clinical Orthopaedics and Related Research 263, pp. 254-262 (1991). According to the Examiner, Sato teaches a device comprising hydroxyapatite, fibrin and BMP. Office Action, pp. 5-6.

Applicants respectfully traverse the rejection in view of the amendments set forth above. Claims 1, 20, and 23 are first discussed.

As amended, these three claims require that the osteogenic protein be purified, i.e., it is not associated with other osteogenic materials with which it is normally associated. However, the BMP used in Sato is a crude bone extract containing bone inductive activity; it contains a myriad of BMPs and other proteins. See, e.g., the paragraph bridging pp. 254-255. In fact, the authors termed this extract "insoluble noncollagenous protein with BMP (BMP-iNCP)." This extract by no means equates to the purified osteogenic protein recited in claim 1. Thus, Sato does not anticipate claim 1, 20 or 23.

The remaining rejected claims all depend from claim 1 or 20 and thus are not anticipated by Sato either.

Applicants further note that the claimed devices are also non-obvious over Sato. Sato's insoluble bone extracts would have been expected by a skilled artisan to possess very different physical properties(e.g., consistency, viscosity, and malleability) from purified (e.g., recombinant) osteogenic protein preparations. The skilled artisan would not have reasonably expected that the handleability of Sato's BMP-iNCP/HAP/fibrin mixture and the ability of this mixture to remain at the defect site and to promote local bone or cartilage formation would be predictive of those

qualities of the claimed devices. Thus, the skilled artisan would not have reasonable expectation of success given Sato's disclosure.

Rejection Under 35 U.S.C. § 102(e)

Claims 1-5, 7, 8-12, 15 and 16 are rejected as allegedly anticipated by Kuberasampath et al., U.S. Patent 5,645,591. According to the Examiner, the '591 patent teaches an osteogenic device containing a collagen-GAG matrix which can further comprise collagen, a methyl cellulose binding agent, and OP-1. Office Action, p. 6. Applicants respectfully traverse this rejection.

Claim 1 is first discussed. This claim, as amended, recites a matrix that is not a synthetic polymer or demineralized bone. However, the matrix material disclosed in the '591 patent is a synthetic polymer.

First, the patent states that the matrix is "a cross-linked polymer of collagen and glycosaminoglycan" (col. 2, lines 43-44; emphasis added). The patent also states "[t]he collagen-GAG polymer is cross-linked to control the solubility and mechanical properties of the matrix" (col. 2, lines 61-67; emphasis added). See also the Abstract and claim 1 of the patent. Second, this cross-linked polymer is synthetic.[2] According to the '591 patent, the collagen-GAG polymer is made artificially by cross-linking collagen and GAG using "chemical, radiation and dehydrothermal methods"

2 "Synthetic" means "prepared or made artificially" (The American Heritage Dictionary of the English Language, 3rd Ed.). "Artificial" means "made by human beings; produced rather than natural." *Id.*

(col. 6, lines 49-56).[3] Therefore, the '591 patent's collagen-GAG polymer does not fall within the scope of claim 1.

The Examiner further alleges that col. 8, ¶ 3 of the patent teaches a collagen-GAG matrix further comprising collagen, as encompassed by claim 1. However, this paragraph describes a method of making the collagen-GAG matrix heavier by adding bovine insoluble collagen. This paragraph does not teach that the added bovine insoluble collagen by itself can form a matrix useful in an osteogenic device. Neither does any other part of the patent. Rather, the added bovine collagen integrates and becomes part of the synthetic, polymeric collagen-GAG matrix. See lines 25-26 of that paragraph. As discussed above, such a collagen-GAG matrix material is a synthetic polymer. The fact that this matrix is a synthetic polymer is not changed by the inclusion of another ingredient.

In sum, claim 1 is not anticipated by the '591 patent. Claims 2-5, 7, 8-12, 15 and 16, all depend from claim 1, and thus are not anticipated by the patent either.

Rejection Under 35 U.S.C. § 103(a)

I

Claims 1, 32, 33, 35 and 36 stand rejected as allegedly obvious over the Kuberasampath's '591 patent. Office Action, p. 7.

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3 The patent teaches that cross-linking is important because it prevents "dissolution of mucopolysaccharide . . . thereby making the materials useful for surgical prostheses, etc." (col. 6, lines 28-31).

Applicants respectfully traverse the rejection. As discussed above, the '591 patent teaches using a synthetic collagen-GAG polymer as a matrix material. The patent does not teach or even suggest the use of any matrix material other than a particular synthetic polymer, much less the use of a matrix material that is not a synthetic polymer. Thus, the patent does not render claim 1 obvious.

For the same reasons, claims 32, 33, 35 and 36 are also non-obvious over the cited art.

II

Claims 1, 13 and 31 stand rejected as allegedly obvious over Kuberasampath's '591 patent, and further in view of Wozney et al. ("Wozney") and Ammann et al. ("Ammann"). Specifically, the Examiner alleges that the '591 patent teaches the device of claim 1, and that Wozney and Amman suggests the use of carboxylmethycellulose ("CMC") and methyl cellulose ("MC") for the same purposes as the device of the '591 patent was intended. Office Action, pp. 7-8.

Applicants respectfully disagree. As discussed in part I, *supra*, the '591 patent does not teach or suggest the device of claim 1. Neither does Wozney or Ammann, as admitted by the Examiner. Thus, a combinantion of these references would not have rendered obvious the device of claim 1 or 13, which depends from claim 1.

As to claim 31, none of the '591 patent, Wozney and Ammann provides any motivation to combine the particular ingredients (OP-1, collagen matrix, and carboxymethylcellulose) recited in the claim. This particular combination of the

ingredients have yielded unexpectedly superior handleability and tissue-inductivity of the claimed device. See applicants' specification at, e.g., p. 86, line 3-5, and p. 87, lines 1-7. None of the references or the combination of these references suggests this unexpected result.

III

Claims 1 and 13 stand rejected as allegedly obvious over Sato in view of Wozney. The Examiner alleges that Sato teaches the device of claim 1 and Wozney teaches the use of CMC. Office Action, pp 8-9.

As discussed above, Sato does not teach the device of claim 1. Neither does it render obvious the device. Wozney does not teach or even suggest the device of claim 1. Thus, a combination of the two references have failed to render obvious the device of claim 1 or 13.

IV

Claims 1, 13, 17-25 and 31 stand rejected as obvious Sato, further inview of Wozney, and further in view of Doll et al. ("Doll"), Cook et al. ("Cook"), Nunez et al. ("Nunez"), Ammann, Alberts, and Reddi.

According to the Examiner, Sato and Wozney together teach the device of claim 1 comprising CMC; Doll teaches that collagen is superior to HA for bone induction; Cook teaches a composite of bovine bone collagen and rhOP-1; Nunez discloses that fibrin glue is a gel; Ammann teaches that CMC can be used for forming a gel; Alberts teaches that collagen-GAG is a highly hydrated, gel-like "ground substance" that allows the migration of cells and cell processes; and Reddi teaches that

biomaterials mimic the extracellular matrix. The Examiner acknowledges that none of Doll, Cook, Nunez, Ammann, Alberts and Reddi teaches the device of claim 1, 13, 17-25 or 31. However, the Examiner alleges that it would have been obvious to use collagen, since it is superior to HA, and CMC, since it forms a gel that could mimic the extracellular matrix.

Applicants respectfully traverse the rejection. Claim 1 is first discussed. As applicants point out in III, *supra*, the combination of Sato and Wozney fails to render the device of claim 1 obvious. Neither does any of Doll, Cook, Nunez, Ammann, Alberts and Reddi -- none of these references teaches (this is acknowledged by the Examiner) or suggests the combined use of an osteogenic protein, a matrix other than a synthetic polymer or demineralized bone, and a binding agent. Thus, claim 1 is distinguished over the combination of the cited art. Consequently, claim 13, which depends from claim 1, is also non-obvious over the art.

Claims 17-25 and 31 all recite the combined use of OP-1, collagen matrix, and CMC. For the same reasons noted above, these claims are also non-obvious since the cited art does not teach such a combination.

For completely, applicants address individually below the secondary references cited by the Examiner (Wozney has been discussed above).

Doll

Contrary to the Examiner's assertion, Doll does not broadly teach that collagen is better than HA for bone induction. Doll merely shows that osteogenin achieves better results in promoting bone regeneration in critical sized craniotomy

defects, when used with type I collagen, as opposed to HA. Applicants note that osteogenin is a bone extract containing a myriad of bone proteins. See, e.g., p. 746, left col., 2nd full ¶. The physical property of such extract would have been thought to be different from that of a protein substantially purified away from other proteins with interfering activities. Thus, while collagen might be better than HA when used with osteogenin, this effect may not be seen with purified proteins. Indeed, Doll suggests that the interaction between osteogenin and its carrier is crucial to the bone inductive activity of osteogenin (p. 747, right col., 3rd and 4th ¶ ¶):

> There may be substantially less binding . . . between the non-resorbable HA and osteogenin. Consequently, the amount of osteogenin protein released into the recipient bed by HA is insufficient to induce bone formation. . . . We may hypothesize that in this treatment, the inductive protein carrier (collagen), released the osteogenin into the recipient bed at the proper time and in sufficient quantity to result in . . . new bone formation.

Thus, Doll does not suggest that collagen is a better carrier than HA when a purified protein, instead of bone extracts, is used. In addition, Doll does not teach the combined use of a purified osteogenic protein, collagen and a binding agent.

Cook

Cook discloses a composite of bovine collagen and rhOP-1. However, this reference provides no motivation to use a binding agent such as CMC in the composite. This deficiency is not remedied by any of the other references cited by the Examiner.

Nunez

This reference discloses that fibrin glue is a gel. However, this references does not provide any motivation to use fibrin glue in conjunction with a purified osteogenic protein such as OP-1 and a matrix other than a synthetic polymer or demineralized bone in inducing cartilage or bone formation. This deficiency is not remedied by any of the other references cited by the Examiner.

Ammann

Ammann describes a TGF-beta composition, using CMC as a carrier. However, this reference does not teach or suggest the additional use of a matrix such as collagen. This deficiency is not remedied by any of the other references cited by the Examiner.

Alberts

This reference is irrelevant. It generally describes the properties of *in vivo*, extracellular matrices (in a physiological context) and does not teach that collagen (exogenous) and a binding agent such as CMC can be used as a carrier for a purified osteogenic protein in a surgical procedure. Further, this reference does not teach that these extracellular matrices can be extracted and used in an osteogenic device. Nor does it teach that even if the matrices can be extracted, they retain the same described physiological properties when placed back into the body. Finally, this reference does not teach that these extracellular matrices would have the biomechanical properties required in a surgical procedure for bone or cartilage repair.

Reddi

This is a review article pointing out the general direction in the bone and cartilage repair field. It does not teach or suggest that bone-inducing proteins can be used in conjunction with a matrix other than a synthetic polymer or demineralized bone and a binding agent such as CMC. This deficiency is not remedied by any of the other references cited by the Examiner.

V

Claims 1 and 6 stand rejected as obvious over Sato as applied to claim 1 and further in view of Ogawa et al. ("Ogawa"), J. Biol. Chem. 267, pp. 14233-14237 (1992). According to the Examiner, Ogawa describes that TGF-β and BMP synergize in promoting the formation of endochondral bone *in vivo*. The Examiner acknowledges that Ogawa does not teach the device of claim 1 comprising two different osteogenic proteins.

Applicants have set forth above that Sato does not teach the device of claim 1. As a result, the combination of Ogawa and Sato does not teach the use of "at least two different osteogenic proteins" in the device of claim 1 or 6, which depends from claim 1. The instant rejection should therefore be withdrawn.

VI

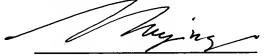
Claims 1 and 14 stand rejected as obvious over Kuberasampath or Sato in view of Wozney and Ammann as applied to claims 1 and 13 above, and further in view of FMC Corporation Bulletin RC-16.

The inapplicability of Kuberasampath, Sato, Wozney and Ammann to claim 1 or 13 has been discussed above. See parts II, III and IV, *supra*. The deficiency of these references is not remedied by the FMC publication, which, as acknowledged by the Examiner, does not teach the device of claim 1 or 13. Thus, the combination of all the cited art does not render obvious claim 1 or 14.

Correspondence Address

Applicants would like to remind the Examiner that a Revocation of Power of Attorney and New Power of Attorney was filed on April 7, 1999. See the enclosed copy (Exhibit 1). The current attorneys for applicants are James F. Haley, Jr., Z. Ying Li, and Karen Mangasarian of Fish & Neave. Testa Hurwitz & Thibeault no longer represents applicants in this case. Please direct all future correspondence in this case to James F. Haley, Jr., at Fish & Neave.

Respectfully submitted,



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